REMARKS

I. Introductory Remarks

The invention is a novel combination of components – a soluble fragment of p75 TNFR, fused to the hinge, CH2 and CH3 domains of a human IgG antibody – as well as polynucleotides that encode this fusion protein and methods of making this fusion protein. The polynucleotides and methods of making are the subject of the present application, while claims to the fusion protein are pending in a sister case, U.S. Appl. No. 08/444,790 ("the '790 application"). The Board of Patent Appeals and Interferences in the '790 application concluded that the "written description supports the pending claim scope." The Board also concluded that "Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection."

There, as here, Applicants submitted overwhelming evidence that the components of the fusion protein ***together each function in a way that is completely different from what would have been predicted.*** For example, the TNFR portion of the combination binds to TNF differently, showing unexpected binding kinetics, affinity and stoichiometry. The immunoglobulin portion of the combination lacks effector functions that it was predicted to retain. This evidence was considered by the Board in the '790 application and the Board's conclusion of non-obviousness applies to the present case.

The claimed subject matter has been pending for nearly eleven years, since 2000. In an effort to expedite prosecution, Applicants began submitting evidence of unexpected results more than six years ago. Despite Applicants' attempts to advance prosecution with multiple in-person interviews, the unexpected results received no substantive consideration until the last Office Action of October 15, 2010 (the "Action").

The Examiner does not dispute that the combination is novel. The Examiner does not even dispute that the properties of the combination are unexpected. Instead, the Examiner has put forth the objection that Applicants have not submitted comparative results against a hypothetical embodiment that the Examiner has only now pointed out, for the first time. In essence, to prove that the properties of the combination are *unexpected*, the Examiner is requiring Applicants to show that this hypothetical embodiment would have its

expected properties. However, the record is clear that the art set forth a clear teaching regarding the expected properties of this hypothetical embodiment and that the prior art would never have predicted the suite of unexpected properties Applicants have demonstrated for the unique and selective embodiments of their claimed invention.

In addition, the Examiner has failed to articulate a rationale for why the combination of the cited references would lead to the claimed invention. In fact, the asserted combination would lead even further from Applicants' claimed invention, and the decision of the Board in the co-pending '790 application regarding non-obviousness applies with even more force here.

The Examiner must articulate a rationale supporting obviousness and must consider all of the evidence presented, direct or indirect. Neither of these requirements has been met in this case. The Examiner has provided no reasoned articulation to select and then alter prior art compounds to reach Applicants' claimed invention, and the Examiner has dismissed Applicants' evidence of unexpected results for reasons that do not withstand logical scrutiny. When the evidence is properly considered, it is clear that the combination recited in the present claims is "more than the predictable use of prior art elements according to their established functions." MPEP §2141(I), citing *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007). As such, the conclusion of nonobviousness is inescapable.

II. Status and Outstanding Rejections

Claims 233-237, 239-243, 246-253, 255-261, and 274-283 are pending. Applicants have added claims 284-286 directed to soluble fragments of the p75 TNFR, which are supported by the written description in the specification according to the Board Decision in the '790 application (see pages 5-6; document D17 on the accompanying SB/08). Applicants reiterate their offer to expedite prosecution by canceling claims 233-237, 239-243, 246-253, and 255-261, should the remaining claims be deemed allowable.

The Examiner withdrew the new matter rejection under 35 U.S.C. §132 with respect to SEQ ID NO: 27, but maintained the rejection with respect to the amendment

making reference to deposited vector PTA 7942. Page 2 of Action. As discussed below, this rejection should be withdrawn in view of the dispositive decision of the Board.

Claims 233-237, 239-243, and 246-252 were rejected under 35 U.S.C. §112, 1st paragraph, for asserted noncompliance with the written description requirement, at page 3 of Action, with respect to: (a) the HL60 cell line deposited under ATCC No. CCL240, in claim 233(b); and (b) the additional subsequences recited in claim 233 (which Applicants have inferred should be a reference to the sequences in claim 234). This written description rejection should be withdrawn for the reasons explained below.

Claims 233-237, 239-242, and 274-279 were rejected under 35 U.S.C. §112, 1st para. for assertedly lacking written description support for the "vast collection of alleles and mutants" and the "undescribed mutants and variants". Page 4 of Action. The Examiner took the position that the term "human TNF receptor" and nucleic acids encoding said molecule encompasses mutants, variants and alleles. Page 6 of Action. As explained below, this written description rejection should be withdrawn in view of the dispositive decision of the Board.

Claims 233-237, 239-243, 246-253, 255-261, and 274-283 were rejected under 35 U.S.C. §103 for alleged obviousness over any one of the following combinations:

(a) Smith et al., U.S. Patent No. 5,395,760 ("Smith Patent"), in view of Capon et al., U.S. Patent No. 5,428,130 ("Capon Patent") (page 7 of Action);

(b) Dembic et al. (Cytokine, 1990; "Dembic") in view of the Smith Patent and the Capon Patent (page 11 of Action);

(c) Smith Patent in view of Hohmann et al. (J. Biol. Chem., 1989) and the Capon Patent (page 12 of Action).

The obviousness rejection under 35 U.S.C. §103 over Smith et al. (Science, 1990) in view of the Capon Patent was withdrawn. Page 10 of Action.

All of the outstanding obviousness rejections should be withdrawn in view of the dispositive decision of the Board, and for the further reasons explained below.

III. Information Disclosure Statement

Submitted concurrently is an information disclosure statement, which includes the Declaration of Taruna Arora Under 37 C.F.R. 1.132 filed in sister case U.S. App. No. 08/444,790 on December 16, 2010. Also submitted herewith is a revised applicant-created form to allow the Examiner to initial that he considered the documents in the IDS previously filed on December 20, 2005. The Examiner rejected the form that was submitted in 2005 because it did not contain certain additional information, in particular the author, intended recipient, and, for documents derived from the files of other patent applications, the inventors and filing date of that other patent application. As Applicants are aware of no rule requiring this data on a form 1449, Applicants submit that the originally filed IDS was fully compliant. Nonetheless, in an effort to expedite prosecution, the requested information is supplied in the form submitted herewith. Applicants request that the Examiner provides an initialed copy of all of these forms.

IV. The Rejection Under 35 U.S.C. §112, first paragraph

A. Plasmid PTA-7942

With respect to the new matter rejection relating to plasmid PTA 7942 (35 U.S.C. §§132 and 112, 1st para., at pages 2 and 4 of the Action), the Board in the '790 application considered the same issue, regarding the same vector, the same amendment, and the same specification. The present application and the '790 application are both continuations of U.S. Appl. No. 07/580,013 and share the same specification.

The Board reversed the new matter rejection, concluding that Dr. Lesslauer's declaration was sufficient to permit verification that the deposited biological material of plasmid PTA 7942 is in fact that disclosed. Page 8 of Board Decision (document D17 on the accompanying SB/08), relating to rejection at pages 20-22 of the Examiner's Answer (document D16 on the accompanying SB/08).

The Board's Decision should be similarly dispositive of the new matter and written description rejections in the present case regarding PTA-7942, and these rejections should be withdrawn.

B. HL-60 cells

The Examiner had previously objected to a number of claims (claims 233-237, 239-243, and 246-252) reciting HL60 cells because they did not identify the particular HL60 cell line and thus assertedly encompassed mutated HL60 cDNA libraries other than those disclosed in the specification. In response, Applicants amended the claims to insert the ATCC deposit number referenced in multiple places in the specification.

Now, the Examiner confusingly takes the position that "the deposited cell line recited [in] the claims [ATCC No. CCL240] is not the specific cell line disclosed in the specification because it is not the specific cell line used by applicant." The Examiner states "none of the cited references provide evidence that the cell line recited in the claims and the cell line used in the specification are identical."

The Examiner's rejection lacks any factual basis. The specification states that HL60 cells deposited under ATCC No. CCL240 were the cells used by Applicants to purify p75 TNFR, and provides evidence that these HL60 cells express a p75 TNFR with all of the amino acid sequences recited in claims 233 and 234.

Example 2 (page 21, line 28 of the specification and following pages) states that HL60 cells identified as ATCC No. CCL240 were cultivated, harvested, and extracted. Example 4 states that the cell extracts obtained according to Example 2 were subjected to affinity chromatography (page 28, line 13) to obtain TNF-binding protein active fractions. Example 5 states that the active fractions obtained according to Example 4 were separated by HPLC (page 29, line 20). Example 6 states that the fractions obtained according to Example 5 were separated by SDS-PAGE (page 29, line 36). Example 7 states that the fractions obtained according to Example 5 were separated according to Example 6 under reducing conditions. Bands cut out from the SDS-PAGE gel were transferred to PVDF membranes, cut out, purified and sequenced. The specification clearly states that the 65/75 kD band (p75

TNFR) contained SEQ ID NO: 10 (page 33, lines 16-17) as well as the other SEQ ID NOs: 12, 8, 9 and 13 recited in the claims (pages 33-34).

Thus, the specification describes a human 75 kD TNF receptor, from HL60 cells identified as ATCC No. CCL240, having all of the characteristics (a), (b) and (c) set forth in claim 233.

C. SEQ ID NOs: 12, 8, 9 and 13

The Examiner's rejection of additional subsequences is believed to refer to the recitation of SEQ ID NOs: 12, 8, 9 and 13 in claim 234. As discussed above, Example 7 shows that the 65/75 kD band (p75 TNFR) contained SEQ ID NO: 10 (page 33, lines 16-17) as well as the other SEQ ID NOs: 12, 8, 9 and 13 recited in the claims (pages 33-34).

Thus, the specification describes a human 75 kD TNF receptor, from HL60 cells identified as ATCC No. CCL240, having all of the characteristics set forth in claims 233-234.

D. Mutants, variants and alleles

With respect to the written description rejection of claims 233-237, 239-242, and 274-279 (35 U.S.C. §112, 1st para., at page 4 of Action) relating to the "vast collection of alleles and mutants" and the "undescribed mutants and variants," the Board in the '790 application considered the same issue and concluded that the "written description supports the pending claim scope." Page 6 of Board Decision, Conclusion of Law.

As in the present case (page 6 of Action), the Examiner in the '790 application had taken the position that the term "human TNF receptor" encompasses allelic variants, and variants with any number of mutations including substitutions, deletions, and additions (page 42 of Examiner's Answer, document D16 on the accompanying SB/08). However, as noted above, the claimed invention is the combination of *known* sequences, not the discovery of novel genes. It is undisputed that such "human TNF receptor" molecules, and the genes encoding them, were well known. The instant application teaches one of skill in the art which p75 TNF receptor sequences to use, and how to test such resulting proteins for binding activity. The same issue was thus squarely before the Board, and the Board reversed the

Examiner. This rejection should be withdrawn in view of the dispositive decision of the Board.

For all of these reasons discussed above in section IV, the various rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

V. The Rejection Under 35 U.S.C. §103

The Examiner rejected the claims as assertedly obvious under 35 U.S.C. §103 in view of a variety of combinations of art: (1) Smith et al., U.S. Patent No. 5,395,760 ("Smith Patent"), in view of Capon et al., U.S. Patent No. 5,428,130 ("Capon Patent" or "Capon '130 patent"), (2) Dembic et al., *Cytokine* 2: 231-237, 1990 ("Dembic") in view of the Smith Patent and the Capon Patent, and (3) the Smith Patent, in view of Hohmann et al., *J. Biol. Chem.* 264: 14927-14934, 1989 ("Hohmann") and the Capon Patent.

A. The Board's conclusion of nonobviousness applies here

The obviousness rejection in the '790 application was based on the same Dembic reference cited by the Examiner in the present case and Capon et al., U.S. Patent No. 5,116,964 (the "Capon '964 patent"). Page 18 of Examiner's Answer (document D16 on the accompanying SB/08). The Capon '130 patent cited in the present case is a continuation of a continuation of the Capon '964 patent, and thus shares the same specification. The Examiner in the '790 application relied upon Dembic for its teaching of the insoluble p75 TNFR and its extracellular domain, and upon the Capon '964 patent for its teaching of Ig/ligand binding fusion proteins. The Capon Patent does not teach the use of a TNFR to make an Ig/ligand binding protein fusion.

In the present case, the Examiner cites the Smith Patent for its teaching of p75 TNFR, its extracellular domain, and a "chimeric antibody molecule" containing a soluble portion of p75 TNFR; and the Capon Patent for its teaching of Ig/ligand binding fusion proteins. Compare pages 8-11 of Action in the present case with pages 18-19 of Examiner's Answer in the '790 application. The combination of the Smith Patent and the Capon Patent leads one of skill in the art even farther from the claimed invention than would the combination of Dembic and the Capon '964 patent. The difference between the two rejections is that the Examiner here relies on the Smith Patent for teaching a "chimeric

antibody molecule" containing a soluble portion of p75 TNFR. However, this chimeric antibody molecule is ***outside*** the scope of the instant claims and leads one of skill in the art away from the claimed invention. Without the disclosure of the Smith Patent (as in the combination of Dembic and the Capon Patent), one of skill in the art would be confronted with the myriad of different formats for Ig/ligand binding fusion proteins disclosed in the Capon Patent with no guidance as to which to choose. ***With*** the additional disclosure of the Smith Patent, one of skill in the art would be directed to a particular format from among this myriad of possibilities, one that is ***outside*** the scope of the claims.

Additionally, the combination of the Smith Patent and the Capon Patent teach against selecting the particular combination recited in the instant claims. The Smith Patent teaches that one can construct a chimeric antibody molecule "having *unmodified constant region domains.*" Smith Patent, col. 10, ln.56-57. An unmodified constant domain of an antibody contains both heavy and light chain sequences and assembles into a very different molecule. Given this explicit teaching to *not* modify the constant domain, one of ordinary skill in the art would be led away from arriving at the protein recited in the current claims, which contains only "all the domains of the constant region of an immunoglobulin heavy chain other than the first domain of said constant region".

Thus, the Smith Patent actively leads away from the claimed embodiment. Therefore, the Board's conclusion that "Appellants' evidence of unexpected results is convincing to rebut the Examiner's obviousness rejection" applies equally, if not with greater force, to the obviousness rejection in the present case. Page 7 of Board Decision, Conclusion of Law.

B. Smith Patent in view of Capon Patent

The combination of the Smith Patent in view of the Capon Patent does not render the instantly claimed invention non-obvious. First, the outstanding Office Action fails to set out a *prima facie* case of obviousness. In particular, no specific reasons for selecting or modifying the purported closest prior art compound were even articulated. Indeed, there are a number of reasons why one would be led away or deterred from selecting the species recited in the claims. Even if one assumes a *prima facie* case, Applicants' overwhelming evidence of unexpected properties mandates a conclusion of nonobviousness. The Examiner

has provided not a shred of evidence to support a contrary conclusion. Instead, the Examiner has provided illogical reasons in an attempt to avoid considering Applicants overwhelming evidence of non-obviousness.

1. No *prima facie* case

It is the Examiner's burden to establish a *prima facie* case of obviousness. Doing so requires a clear articulation of the rationale for obviousness, and the factual findings supporting the rationale. In particular, where the obviousness case relies upon selection and modification of a prior art embodiment or "lead compound", as it does here, the Examiner must explain the ***specific reason to select*** the lead compound, *and* ***the specific reason for modifying*** this prior art compound, as well as the predictability of the result. See the "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex", 75 *Fed. Reg.*, No. 169, page 53643 et seq., September 1, 2010 ("2010 KSR Guidelines Update"), e.g., page 53652, 1st col. ("there must be some reason 'to select and modify a known compound'").

a. No articulated reason to select the chimeric antibody molecule of the Smith Patent, and no incentive prompting its modification

The Court of Appeals for the Federal Circuit has stated that "post-KSR, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). The Examiner has specifically cited col. 10, last paragraph of the Smith Patent as teaching such a lead compound. It contains a "soluble portion of a 75 kD TNF receptor" and is "produced from a single heavy constant and light chain constant region" of IgG1. Page 10 of Action. As explained below, when the molecule is produced, two identical heavy chains will assemble with two identical light chains to form a covalently linked tetramer.

However, "there must be some reason for starting with that lead compound other than the mere fact that the 'lead compound' merely exists." *2010 KSR Guidelines*

Update, page 53652, 1st col. The primary focus of the Smith Patent is the cloning of p75 TNFR DNA (Example 2), and the expression of various soluble fragments in Examples 3-8. While the Smith Patent contemplates dozens of conjugates and fusion proteins, none were made.

The Examiner provided ***no articulated rationale*** for selecting the chimeric antibody molecules, in particular, from among the variety of conjugates of TNFR described at col. 10 of the Smith Patent. The list includes tandem repeats joined by a linker (displaying 2 TNF-R fragments), as well as conjugates to polymers, polyethylene glycol, dextran, biotin-avidin (displaying 4 TNF-R fragments), dinitrophenol and trinitrophenol (displaying 10 TNF-R fragments). In fact, it appears that only hindsight, with knowledge of the claimed invention, guided the Examiner's selection of this molecule.

No proper *prima facie* case of obviousness can be made if the beginning step, a reasoned identification of a lead compound, is missing. The mere fact that a compound exists is not a sufficient reason to select it. Here, a chimeric antibody molecule of the Smith Patent does not even exist, since it is a purely hypothetical description, and no reason at all has been articulated for selecting it.

Moreover, there is no specific reason or incentive prompting modification of the molecule, which contains two light chains covalently bound to the heavy chains, to remove the CH1 domains of the heavy chains, and the light chains, so as to arrive at the homodimeric fusion protein recited in the claims. At best, the ordinary skilled artisan reading the two cited references together would select the chimeric antibody molecules described in the Capon Patent that are the same as those described in the Smith Patent. Such embodiments contain not only the CH1 domains of the heavy chains but also light chains covalently linked to the heavy chains through disulfide bonds; polynucleotides encoding these proteins are clearly ***outside*** of the scope of the presently pending claims. Indeed, as noted above, given the teaching in Smith to use unmodified antibody constant regions, one of skill would be deterred from then *modifying* the constant region by removing particular domains and the light chain.

The rejection failed to articulate a specific reason or incentive prompting further modification of these chimeric antibody molecules to remove the CH1 domains of the heavy chains and remove the light chains in their entirety. The Federal Circuit has stated that "in cases involving new chemical compounds, ***it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner*** to establish prima facie obviousness of a new claimed compound." *Eisai, supra,* 533 F.3d 1353, 1359 (quoting *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)) (emphasis added).

In fact, the ordinary skilled person, having prepared the chimeric antibody molecule of Smith in pursuit of increased valency and ***increased*** number of TNF-R binding sites, would be ***deterred*** from ***reducing*** the number of TNF-R units in the molecule. Thus, there is no articulated motivation for the ordinary skilled person to modify a chimeric antibody molecule of the Smith Patent, which apparently contains ***four*** TNF-R fragments, to produce a protein consisting of a homodimeric heavy chain that has no more than ***two*** TNF-R fragments. [1]

No proper *prima facie* case of obviousness can be made if the motivation or incentive for modifying the prior art compound is missing.

b. Combining the Smith Patent and the Capon Patent teaches away from the claimed combination

Even if, for the sake of argument, one assumes selection of the tetrameric chimeric antibody molecule described in the Smith Patent, combining that disclosure with the Capon Patent does not arrive at the claimed invention. The combination leads to the same tetrameric chimeric antibody molecule disclosed in each of these references, and ***away*** from the homodimeric fusion proteins recited in the claims.

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[1] Applicants note for the record that the Examiner has not explicitly pointed out the precise structure of the chimeric antibody molecule in the Smith patent he identifies as the closest prior art. Given the Examiner's reference to the fusion protein in Smith that is "bivalent for TNF receptor", and that this reference appears in the sentence describing a molecule with four TNF-Rs, Applicants must assume that this is the embodiment asserted as the closest prior art. However, no matter which embodiment in the Smith Patent is asserted, the prima facie case of obviousness still fails.

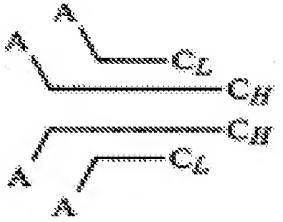
The portion of the Smith Patent cited by the Examiner is reproduced below:

> For example, chimeric TNF-R/IgG1 may be produced from ***two chimeric genes*** – a TNF-R/human κ light chain chimera (TNF-R/Cκ) ***and*** a TNF-R/human γ1 heavy chain chimera (TNF-R/Cγ-1). Following transcription and translation of the two chimeric genes, the gene products assemble into a single chimeric antibody molecule having TNF-R displayed bivalently. [Col. 10, lines 57-64, Smith Patent; emphasis added.]

While the Examiner characterizes this as "bivalent (aka it contains only two copies of the TNF R molecule" (page 10 of Action), following these instructions in the Smith Patent necessarily and inevitably produces a tetramer. Two identical heavy chain chimeras will assemble with two identical light chain chimeras just as they do in a natural antibody molecule.

Confirmation that these instructions lead to such a tetrameric molecule is found in the two references cited at col. 10, lines 66-68 of the Smith Patent for "details relating to the construction of such chimeric antibody molecules." Each of these two documents, WO 89/09622 and EP 315062, describe constructing chimeric antibody molecules in which the native variable regions have been replaced with other antigen-binding regions, to produce chimeric antibody molecules that contain two heavy and two light chains. The Capon Patent itself confirms the understanding in the art that chains of the hybrid immunoglobulins will be "***disulfide bonded in the same fashion as native immunoglobulins***." Capon Patent, col. 11, lines 36-38 (emphasis added).

Thus, the chimeric IgG1 antibody molecule specifically described at col. 10, last paragraph of the Smith Patent is ***the same as*** the tetramer depicted at col. 11, lines 15-20 of Capon Patent, wherein the designation "A" represents a ligand binding partner substituted for the variable domains of an immunoglobulin:



The Capon Patent states: "The hybrid immunoglobulins of this invention are also ***constructed in a fashion similar to chimeric antibodies*** in which a variable domain from an antibody of one species is substituted for the variable domain of another species." Capon Patent, col. 15, lines 9-25 (emphasis added). The Capon Patent explicitly states that one of its ***preferred*** embodiments is this type of fusion protein where the ligand binding partner is substituted for the variable region of the immunoglobulin:

> In a ***preferred embodiment*** in which the stable plasma protein is an immunoglobulin chain, the ligand binding partner will be substituted into at least one chain, and ordinarily for the ***variable region*** of the immunoglobulin or suitable fragment thereof. [Col. 5, lines 37-41; emphasis added.]

MPEP §2144.08 states that the Examiner is obligated to "consider any teaching or suggestion in the reference of a ***preferred species or subgenus that is significantly different in structure from the claimed species or subgenus***. Such a teaching may weigh against selecting the claimed species or subgenus and thus ***against*** a determination of obviousness." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16 F.3d at 382-83). For example, MPEP §2144.08 cites *Baird* for the example that "teachings of preferred species of a complex nature within a disclosed genus may motivate an artisan of ordinary skill to make similar complex species and thus teach away from making simple species within the genus." MPEP §2144.08(II)(A)(4)(c) (citing *In re Baird*, 16 F.3d at 382).

Consequently, the combination of references teaches away from Applicants' claimed species and weighs against a determination of obviousness.

c. Reasons not to select a homodimeric embodiment from the hundreds disclosed in the Capon Patent

If the rationale for modifying the tetramer described in the Smith Patent is merely that it could theoretically be replaced by any of the embodiments described in the Capon Patent, this rationale also fails. The selection of a single species from a generic disclosure encompassing hundreds, if not thousands, of species is not obvious, particularly where the art teaches away from such a selection. The mere fact that a modification might be possible is not a reason to select it. There were many reasons to prefer embodiments ***other***

than those recited in the claims, and there were good reasons ***deterring*** the selection of the embodiments recited in the claims.

Column 12, line 1 to column 14, line 40 of the Capon Patent displays over two hundred and fifty different general formats for Ig/ligand binding protein fusions, which are completely unlimited with respect to the identity of the ligand binding portion of the fusion protein. Thus, in total, the disclosure in the Capon Patent encompasses at least thousands of fusion proteins. The Capon Patent discloses fusion of receptor fragments to immunoglobulin fragments of varying lengths and with varying conformations, including monomeric, homodimeric, heterodimeric, trimeric, tetrameric, homomultimeric and heteromultimeric forms. [Col. 11, lines 1-35, col. 11, lines 52-55, col. 13, lines 18-21.] The disclosed fusions can contain a variety of immunoglobulin constant region fragments, such as the entire constant region (CH1-hinge-CH2-CH3), hinge-CH2-CH3, CH2-CH3, or the light chain constant region (CL). [Col. 10, lines 19-25.]

As noted above, embodiments containing the CH1 domain, in which the ligand binding partner is substituted for the variable region, are "preferred" embodiments. Capon Patent, col. 5, lines 37-41. The Smith Patent teaches that the chimeric antibody molecules have "unmodified constant regions," thus expressing a preference for an embodiment that comprises the CH1 domain. Smith Patent, col. 10, lines 57-61. The combination of the cited references ***teaches away*** from the particular species of fusion proteins encoded and produced by the claimed polynucleotides.

Further, there were additional reasons not to select a homodimeric fusion protein containing TNFR and hinge-CH2-CH3 for therapeutic or non-therapeutic uses. One would not select such a fusion protein for a therapeutic use because the TNFR portion would be expected to have the effect of suppressing inflammation, whereas the hinge-CH2-CH3 would be expected to retain pro-inflammatory effector functions. Smith Patent, col. 16, lines 60-66; Capon Patent, col. 4, lines 45-49. Such a molecule would not be expected to be appropriate for use in conditions characterized by either excess inflammation or a need for a more robust immune response.

One would not select such a fusion protein for an *in vitro,* non-therapeutic use since one could not be certain it would even bind to TNF. "Lesslauer Declaration A"; Exhibit G to Applicants' response filed September 8, 2010 and also previously submitted December 9, 2004. Deletion of the hinge region, which is responsible for disulfide bonding and resulting dimerization of the protein, would also have been desirable from the standpoint of eliminating a part of the constant region that is involved in pro-inflammatory effector functions. Moreover, enhanced plasma half-life, the primary motivation for immunoglobulin fusions according to the Capon Patent, would be completely irrelevant for *in vitro* uses. Capon Patent, col. 1, lines 13-16.

There would have been a good rationale for selecting a monomeric form, in order to maximize the likelihood of binding to trimeric TNF. Dimeric or other multimeric forms may have had a spatial geometry that prevented high affinity binding to the trimeric TNF ligand, as stated in the Declaration Under 37 C.F.R. 1.132 of Dr. Werner Lesslauer ("Lesslauer Declaration A"; Exhibit G to Applicants' response filed September 8, 2010 and also previously submitted December 9, 2004).

Thus, there were many reasons to prefer embodiments *other than* those recited in the claims and no specific incentive to select the particular embodiments recited in the claims. In view of all of the reasons discussed above in sections 1.a.-1.c., the Examiner has failed to establish a proper *prima facie* case of obviousness.

2. Unexpected results

The Examiner relies on predicted properties of fusion proteins taught by the Capon Patent for an alleged motivation to construct the claimed polynucleotides. The Examiner states that "fusion proteins have a variety of a uses (see column 4 [of Capon])." Action at page 8. The cited portion of Capon describes, among other uses, that "[i]t is an object of the invention to provide novel hybrid immunoglobulin molecules which combine the adhesive and targeting characteristics of a ligand binding partner with immunoglobulin effector functions such as complement binding, cell receptor binding, and the like." Capon, col. 4, lines 38-47. Thus, the Action implicitly admits that proteins encoded by the claimed

polynucleotides would have certain expected properties, such as effector functions, and relies on these expected properties of the protein to support the rejection.

Against this background of expected properties, Applicants have submitted overwhelming evidence of ***unexpected*** properties in ***multiple*** different categories. This evidence shows that the components of the fusion protein, when together, function in a way that could not have been predicted. The p75 TNFR portion of the combination binds differently, with unexpected binding kinetics, affinity and stoichiometry. The immunoglobulin portion of the combination unexpectedly lacks effector functions and aggregation ability that it was predicted to retain. The combination demonstrates a 1000-fold improved TNF neutralization potency compared to monomeric soluble TNFR.[2] The Action does not dispute the unexpected nature of these results and makes no attempt to show that these components are acting "according to their established functions." *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007). In view of this, a conclusion of nonobviousness is inescapable.

a. It would be reversible error to ignore unexpected properties of the encoded protein

The Examiner has only reluctantly considered Applicants' evidence of unexpected results, and continues to take the position that "[t]here is no evidence of record regarding unexpected results and the claimed invention (aka nucleic acids)." Page 8 of Action. Applicants request ***withdrawal*** of these comments because it would be reversible error to ignore unexpected properties of the encoded protein.

It is well settled that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP §2143.03, citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). The protein encoded by the polynucleotides is specifically recited in all of the pending claims; thus, unexpected results with respect to the protein must be considered. Even the Examiner has acknowledged this by

[2] See Mohler *et al.*, *J. Immunol.*, 151:1548-1561, 1993 (Exhibit I to Applicants' response filed September 8, 2010 and previously submitted 2004) at Figures 2A-B. Fusion to an immunoglobulin fragment was not expected to change potency. Prior art CD4-immunoglobulin fusions exhibited "the same potency as soluble rCD4." Capon, *Nature*, 337:525-531,1989 (Exhibit J to Applicants' response filed September 8, 2010 and previously submitted in 2007) at page 526, 2nd col., Table 1 at page 527, and page 529, 2nd col.

relying on the expected properties and projected uses of the encoded protein to support the obviousness rejection. See page 8 of the Action. If the properties of the protein are used in an attempt to support the rejection of claims to polynucleotides, they cannot be ignored in judging patentability of the polynucleotides and methods of using them.

"All evidence, including evidence rebutting a *prima facie* case of obviousness, must be considered when properly presented." *2010 KSR Guidelines Update*, 75 Fed. Reg. 53657 (2010) (citing *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007)). In *Sullivan*, the Board had refused to consider Applicants' rebuttal evidence because it considered the evidence to relate to the intended use of the claimed composition, rather than the composition itself. The Federal Circuit reversed the Board, holding that the use and unexpected property was relevant and cannot be ignored. Similarly, here, the unexpected properties resulting from the use of the claimed polynucleotides to make proteins is relevant and cannot be ignored.

The unexpected properties of the encoded protein are also highly relevant to Applicants' claims directed to processes of producing the protein. MPEP §2116.01 states that "all the limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining the obviousness of a process or method claim." MPEP §2116.01 also states that "proper claim construction requires treating language in a process claim which recites the making or using of a nonobvious product as a material limitation." Since the making of a nonobvious product must be treated as a material limitation, unexpected results associated with that product are necessarily relevant to the process claim.

The patent statutes explicitly contemplate that patentable processes include new uses of *known* processes (see 35 U.S.C. §100(b) "The term "process". . . includes a new use of a known process"). Moreover, 35 U.S.C. §103(b) requires that a biotechnological process resulting in a novel and nonobvious composition of matter shall be considered nonobvious. Thus, an otherwise known and conventional process can be patented if limited to making or using a nonobvious product. In the present case, the process claims must be patentable because they use a novel and nonobvious polynucleotide, not found in nature or the prior art, to produce a novel and nonobvious product, also not found in nature or the prior art.

For all of these reasons, it would be clear legal error to take the position (as at page 8 of the Action) that, because the claims relate to nucleic acids, there is no evidence of record regarding unexpected results for the claimed invention. Unexpected properties of the encoded protein are highly relevant, and the error and inconsistency of the Examiner's reasoning is highlighted by his attempt to rely on the protein and its properties to support the rejection.

b. Applicants' uncontradicted evidence mandates a conclusion of nonobviousness

i. Expected properties of the chimeric antibody molecule cited by the Examiner include effector functions and aggregation ability

The hypothetical TNF-binding IgG1 chimeric antibody molecule at col. 10, last paragraph of the Smith Patent is cited by the Examiner as the purported closest prior art embodiment. Pages 9-10 of Action. This molecule, like other proteins which retain the hinge, CH2 and CH3 domains of an immunoglobulin, would have been expected to retain antibody effector function. Capon Patent, col. 4, lines 45-49. Moreover, this chimeric antibody molecule, like other antibodies, would have been expected to retain the ability to form aggregates with the trimeric TNF ligand. *See, e.g.,* Winzor et al., Arch. Biochem. Biophys. 268(1): 221-226 (1989) (Exhibit 3 hereto and document D40 on accompanying SB08).

The Examiner does not dispute that the ordinary skilled person would have expected fusion proteins which comprise the hinge, CH2 and CH3 domains of an immunoglobulin to retain effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). As noted above, the Examiner relies on the expected properties of the encoded proteins to support the obviousness rejection, citing col. 4 of the Capon Patent.

The portion of the Capon Patent cited by the Examiner teaches that its hybrid immunoglobulin fusion proteins were expected to retain immunoglobulin effector functions.

See, e.g., col. 4, lines 45-49, and col. 14, lines 61-68. It was well known that the binding sites for the proteins that initiate ADCC and CDC (FcγRs and C1q, respectively) are within the CH2 domain, for C1q, or in the region linking the hinge to CH2 domains, for FcγRs. *See, e.g.,* Capon, *Nature* 337: 525-531, 1989 (Exhibit J to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007) at page 528, 1st col.

Consistent with this teaching and expectation, prior art references confirmed that dimeric fusion proteins consisting of hinge, CH2 and CH3 domains fused to CD4 fragment retain effector functions.[3] Similarly, other dimeric fusion proteins containing CH1, hinge, CH2 and CH3 domains fused to IL-2 show "maintenance of Ig effector function." [4]

The references cited in the Smith Patent for instructions on preparing chimeric antibody molecules also teach that such molecules would retain effector functions. See WO 89/09622 (page 7, lines7-15) and EP 315062 (page 2, lines 37-42, page 3, lines 51-54 and page 15, lines10-32), each cited at col. 10, line 68 of the Smith Patent. Consistent with this expectation in the art, Applicants showed that the anti-TNF chimeric antibody molecule infliximab retains full effector functions.[5] The Examiner does not dispute this data.

Moreover, it was well known in the art that multivalent antibodies are expected to form aggregates with multivalent ligands, such as the trimeric TNF ligand. See Winzor et al., Arch. Biochem. Biophys., 268(1): 221-226 (1989) (Exhibit 3 hereto and document D40 on accompanying SB/08) (in interactions between bivalent antibodies and multivalent antigen, binding of antibody to antigen forms aggregates that are "extensively crosslinked" [see footnote 2] and so large that they precipitate). Consistent with this expectation in the art, Applicants showed that the anti-TNF chimeric antibody molecule

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[3] See Byrn et al., *Nature* 344: 667-670, April 1990 (Exhibit H to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007) at page 668, 1st col., and Fig. 2 at page 669 (ADCC retained); Traunecker, *Nature*, 339:68-70, 1989 (Exhibit K to Applicants' response filed September 8, 2010 and previously submitted in 2007) at page 69, 1st col. and Fig. 3 (FcγR and C1q binding retained).

[4] Landolfi, 146(3), 915-919, Feb. 1991 (submitted herewith **as Exhibit ****) at the paragraph bridging page 917-918. Such later-published art, like declaratory evidence, can be considered for relevancy to a scientific fact or principle. *Cf. In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (C.C.P.A. 1974); *In re Wilson*, 311 F.2d 266, 268-269, 135 USPQ 442, 444 (C.C.P.A. 1962).

[5] See Figures 8 and 9 of Kohno for FcγR-binding and C1q-binding, respectively (Exhibit L to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007); Figures 3 and 4 of Khare for ADCC and CDC, respectively (Exhibit M to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007).

infliximab retains the ability to aggregate with TNF into multi-unit complexes.[6] The Examiner does not dispute this data.

Thus, a multitude of evidence shows that the ordinary skilled person would have expected a TNF-binding chimeric antibody molecule of the Smith Patent to retain antibody effector function, like other immunoglobulin hybrid fusion proteins which retain hinge, CH2 and CH3 domains. Evidence also shows that the ordinary skilled person would have expected a TNF-binding chimeric antibody molecule of the Smith Patent to retain the ability to form aggregates with the trimeric TNF ligand.

ii. Evidence that the fusion proteins recited in the claims lack predicted effector functions and aggregation ability

The fusion proteins encoded and produced by the claimed polynucleotides would have been expected to retain effector functions, like other proteins that retain hinge, CH2 and CH3 domains. The fusion proteins would also have been expected to retain the ability to aggregate with trimeric TNF, like other interactions between bivalent antibodies and multivalent antigen. The Examiner has provided absolutely no evidence, reasoning or even speculation to show otherwise.

In contrast to this established expectation, Applicants provided uncontested evidence that a p75 TNFR-immunoglobulin fusion protein encoded and produced by the claimed polynucleotides exhibited unexpected properties in a number of different categories, including FcγR-binding, C1q-binding, ADCC, CDC, aggregation ability, and binding stoichiometry. See Kohno (Exhibit L to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007); Khare (Exhibit M to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007); Declaration of Taruna Arora Under 37 C.F.R. 1.132 ("Arora Declaration"; submitted as Exhibit 2 and document D15 on accompanying SB/08) and Barone (Exhibit N to Applicants' response filed September 8, 2010 and previously submitted August 30, 2007):

[6] Figure 6 of Kohno shows formation of high molecular weight aggregates and a precipitation line in the classic Ouchterlony test; Figures 3 and 4 of Kohno show high molecular weight aggregates and binding stoichiometry in which 3 or more antibodies bind 3 or more TNF trimers.

(a) Etanercept displayed ***no difference in binding to FcγRs*** in the presence and absence of TNF, in contrast to the many-fold increase in binding seen for infliximab and another anti-TNF antibody. Figure 8 of Kohno. FcγRs are the receptors that mediates ADCC.

(b) Etanercept displayed ***no binding to C1q above background levels*** in the presence or absence of TNF, in contrast to the many-fold increase in binding seen for infliximab and another anti-TNF antibody in the presence of TNF. Figure 9 of Kohno. Binding to C1q initiates CDC.

(c) Etanercept displayed ***markedly reduced levels of ADCC*** as compared to an antibody. Figure 3 of Khare; also Exhibit D of Arora Declaration. Since ADCC is pro-inflammatory, the absence or marked reduction in this activity is advantageous when treating inflammatory disorders.

(d) The Barone reference reports that etanercept is ***unable to mediate CDC***. Barone ("etanercept was not able to mediate complement-dependent killing"). Data in the Arora Declaration shows that etanercept exhibits no detectable CDC activity at most concentrations (5/7) tested, and markedly reduced CDC activity at the two highest concentrations. Exhibit C of Arora Declaration. Figure 4 of Khare also shows that etanercept exhibits markedly reduced CDC activity. Since CDC is pro-inflammatory, the absence or marked reduction in this activity is advantageous when treating inflammatory disorders.

(e) Etanercept ***does not aggregate or precipitate*** TNF in the classic Ouchterlony test. Figure 6 of Kohno.

(f) Etanercept ***does not form high molecular weight multi-antigen complexes.*** Etanercept exhibits a primarily 1:1 binding stoichiometry in the presence of excess TNF. Figure 2 of Kohno. A 2:1 etanercept:TNF complex can be formed in the presence of excess etanercept. Figure 5 of Kohno. No complexes were observed in which one molecule of etanercept

bound two TNF trimers. Since deposition of antigen:antibody aggregates was known in the art to be pathogenic, the absence of the ability to form such aggregates is advantageous when treating inflammatory and other disorders.

These data show that the TNFR portion of the combination functions differently because it binds with unexpected stoichiometry, and the immunoglobulin portion of the combination functions differently because it lacks expected effector functions in a number of different categories. The combination also functions differently than predicted because it lacks aggregation ability.

The Examiner ***does not dispute the unexpected nature of these results***. In fact, the Examiner implicitly acknowledges that these are unexpected by his reliance on the presence of effector functions as purported motivation to make "fusion proteins with a variety of a uses (see column 4 [of Capon])." Office Action at page 8. Instead, the Examiner complains that the comparator infliximab was a chimeric antibody molecule that is structurally different because it does not contain TNFR (i.e., binding is mediated by murine variable regions instead of a TNFR fragment). Page 10 of Action. This comment is completely irrelevant to the results. If one views infliximab merely as a positive control, the results with respect to etanercept stand alone as uncontroverted evidence of properties that are ***completely different from what would have been predicted***.

In addition, the Examiner questioned the amino acid sequence of the etanercept tested in Kohno, Khare and Barone. Page 10 of Action. However, there is no doubt that this protein is encoded and produced by the claimed polynucleotides. Applicants previously provided evidence that etanercept "is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain of IgG1. [Page 14 of Enbrel US Product Insert (Exhibit Q to Applicants' response filed September 8, 2010).] The amino acid sequence of etanercept is reported in the United States Adopted Names (USAN) Council report, *Clin. Pharm. & Ther.*, vol. 66, no. 2, August 1999, at page 209 (Exhibit 1 hereto and document D42 on the accompanying SB/08).

Moreover, it is likely that at least some of these unexpected properties of etanercept described above correlate to differences in clinical efficacy and safety between etanercept and anti-TNF-α antibodies. Researchers in the field have drawn links between some of these mechanistic differences in binding stoichiometry/effector function, and differences in clinical efficacy and safety. Granulomatous infectious diseases occur at a greater frequency in patients treated with infliximab, an anti-TNF-α antibody, as compared to patients treated with etanercept. Wallis et al. (2004), Clin. Inf. Dis. 38: 1261-1265 (Exhibit 4 hereto and document D38 on accompanying SB/08); Wallis et al. (2005), Clin. Inf. Dis. 41(Suppl 2): S1-S5 (Exhibit 5 hereto and document D37 on accompanying SB/08). With regard to this observed difference, one group of researchers comments, "[I]t is possible that the combination of high avidity binding to mTNF within the granulomatous tissue, and the ***ability to bind FcγR and C1q as large Ab complexes***, may account for the higher rates of granulomatous infections in patients treated with the anti-TNF mAbs." Arora et al. (2009), Cytokine 45: 124-131 (Exhibit 6 hereto and document D26 on accompanying SB/08) (emphasis added). Other authors have made the following observations:

> Infliximab induces complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity in a murine myeloma cell line expressing membrane-associated TNF (67). Macrophages and monocytes are among the cells that express membrane-associated TNF. The monocytopenia observed in patients following treatment with infliximab that can persist for weeks following infusion (68) may reflect direct killing of cells expressing membrane-associated TNF by infliximab. This has clinical implications because monocytes are an essential component of granulomas; monocyte elimination might lead to susceptibility to granulomatous diseases. , , , Etanercept contains the Fc portion of IgG1, but reportedly ***does not fix complement*** (69), perhaps because steric hindrance prevents C1q binding, which initiates the classical complement cascade. Furthermore, because etanercept ***binds only single molecules of TNF, it is unlikely to form aggregates*** that can activate complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity. [Emphasis added.]

Furst et al. (2006), Semin. Arthritis Rheum. 36: 159-167, at page 164 (Exhibit 7 hereto and document D41 on accompanying SB/08).

Other authors have also commented on the possible relationship between mechanistic differences in binding stoichiometry/effector function and safety profile, in particular, reactivation of herpes zoster and tuberculosis. Strangfeld et al. (2009), JAMA 301(7): 737-

744 (Exhibit 8 hereto and document D22 on accompanying SB/08). Thus, some of the properties that Applicants' have reported as unexpected results have been hypothesized by researchers to be related to the different clinical efficacy and safety profiles of anti-TNF-α antibodies as compared to etanercept.

In summary, Applicants have submitted an abundance of evidence demonstrating the expectation in the art that a TNF-binding chimeric antibody molecule of the Smith Patent would retain effector functions. The Examiner has provided no evidence or even speculation to prove otherwise. Although ***a single unexpected property is sufficient for a showing of nonobviousness,*** Applicants have submitted overwhelming, uncontradicted evidence showing that fusion proteins encoded by the claimed polynucleotides and expressed by the claimed methods have unexpected properties in ***more than six different categories***, such as FcγR-binding, C1q-binding, ADCC, CDC, aggregation ability and binding stoichiometry. Moreover, researchers in the art have opined that some of these unexpected properties may be related to the clinical safety and efficacy profile of etanercept. Applicants' demonstration of unexpected results rebut the outstanding obviousness rejections, and they should be withdrawn.

iii. Similar molecules that are outside the scope of the claims fail to show certain of these unexpected properties

Applicants have shown that this marked reduction in effector functions is not due to the unique nature of the TNF ligand, because chimeric antibody molecules that bind TNF exhibit effector function (e.g., infliximab). The marked reduction in effector functions cannot be due to the homodimeric configuration, because Applicants have evidence showing that a number of homodimeric fusion proteins containing the CH2 and CH3 domains *retain effector function* (e.g., homodimeric fusion proteins containing CD4, IL-2, and even p75 TNFR fragments [see Arora Declaration]).

Marked reduction in effector functions does not appear to merely be due to the presence of p75 TNFR fragments in the molecule. This conclusion is supported by scientific results presented in the Declaration of Taruna Arora under 37 C.F.R. 1.132 (Exhibit 2,

submitted herewith and D15 in the accompanying SB/08). These results confirm Applicants' prior evidence that an embodiment within the scope of Applicants' claims, etanercept, shows unexpected properties when compared to TNF-binding proteins that fall outside of the scope of Applicants' claims. The etanercept embodiment was compared to two different anti-TNF antibodies and two different fusion proteins, Delta 57 and Protein 3.5D. Delta 57 and Protein 3.5D contain fragments of the p75 TNFR extracellular region (amino acids 1-179 and 1-163 of the mature amino acid sequence, respectively), a linker of 27 amino acids, and only a portion of a hinge domain. Both are missing the first several amino acids of this domain, and thus do not comprise "all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain". In these experimental results, the two anti-TNF immunoglobulins and the Delta 57 and Protein 3.5D fusion proteins did not exhibit the same, consistent, and surprising lack of complement mediated cytotoxicity and antibody dependent cellular cytotoxicity that was shown by etanercept. Thus, these homodimers which comprise a TNF binding p75 TNFR fragment retained effector function. The only reasonable conclusion that can be drawn is that Applicants' evidence of unexpected results is due to the claimed combination of features, and therefore the claimed polynucleotides and recombinant expression methods are nonobvious.

Unexpectedly superior properties (MPEP §716.02(a)(II)), "presence of a property not possessed by the prior art" (MPEP §716.02(a)(III), citing *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963)), and the "[a]bsence of property which a claimed invention would have been expected to possess based on the teachings of the prior art [are] evidence of unobviousness" (MPEP §716.02(a)(IV), citing *Ex parte Mead Johnson & Co.*, 227 U.S.P.Q. 78 (Bd. Pat. App. & Inter. 1985). Even if the claimed invention possesses a ***known property*** predicted by the prior art, the ***presence of a second unexpected property renders it nonobvious***. MPEP §716.02(c)(I), citing *In re May*, 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978) (although claimed compound had expected analgesic effect, evidence that the compound was also unexpectedly nonaddictive was sufficient to overcome obviousness).

When considered and given due weight, Appellants' evidence of unexpected results in a multitude of different categories rebuts any possible case of obviousness and requires reversal of the rejection under 35 U.S.C. §103. "[W]hen an applicant demonstrates

substantially improved results . . . and ***states*** that the results were ***unexpected***, this should suffice to establish unexpected results ***in the absence of*** evidence to the contrary." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (emphasis in original).

iv. The Examiner failed to consider Applicants' evidence with respect to other IgG types

The Examiner failed to consider Applicants' evidence with respect to other IgG types. The Examiner asserted at page 10 of the Action that results related to etanercept are not germane to constant regions other than IgG1, yet the Examiner did not consider and address Applicants' evidence with respect to IgG3 fusions.

Lesslauer and coworkers demonstrated that a fusion of soluble p75 TNFR to the hinge region of IgG3 exhibited (a) surprisingly good binding affinity, (b) unexpectedly higher kinetic stability, and (c) improved inhibition of TNF biological activity. See Lesslauer Declaration A (Exhibit G to Applicants' response filed September 8, 2010 and also previously submitted December 9, 2004).

In the declaration, Dr. Lesslauer states: "Surprisingly, however, the fusion construct obtained even had an excellent binding activity. In addition, an unexpectedly higher kinetic stability and a surprisingly improved inhibition of the effect of TNF in biological cell culture tests were discovered as well." In particular, the figure shows that, at the six-minute time point, essentially all of the TNFα had dissociated from the monomeric p75sTNFR, while only about half of the TNFα had dissociated from the dimeric p75sTNFR fusion. The figure indicates that the dimeric product binds for a longer period of time and has a higher kinetic stability than the monomeric product.

Such an improvement in dissociation kinetics and potency was unexpected and had not been observed for prior art immunoglobulin fragment fusions. For example, Capon (1989) stated that the dissociation constant of the fusion was "indistinguishable from that of soluble rCD4" and exhibited "the same potency as soluble rCD4." Capon (1989) (Exhibit J to Applicants' response filed September 8, 2010) at page 526, 2nd col., Table 1 at page 527, and page 529, 2nd col.

Thus, this data shows unexpected results in three different categories. The data clearly show that the combination of components functions in ways not predicted. Consistent with the data for IgG1 embodiments, the data for the IgG3 embodiments show that the TNFR portion of the combination binds in a different manner with unexpected kinetics and stoichiometry. It is ***reversible error*** for the Examiner to fail to consider and comment on Applicants' evidence. *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *2010 KSR Guidelines Update* 75 Fed. Reg. at 53657.

c. All of Applicants' evidence must be considered, whether direct or indirect

The claimed subject matter has been pending for over 11 years. Applicants began submitting evidence of unexpected results over six years ago, and have attempted to expedite prosecution with numerous personal contacts and interviews. Applicants provided evidence of unexpected results in more than six different categories, when only *one* unexpected property suffices to render the claimed invention nonobvious.

The Examiner does not dispute that the properties of the combination are unexpected. Instead, the Examiner objects that Applicants have not submitted results of a direct comparison to a hypothetical "paper" embodiment in the Smith Patent that the Examiner has only now pointed out for the first time. Page 9 of Action. This is manifestly inappropriate. First, "[A]pplicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." MPEP §716.02(e)(III).

But more importantly, the Examiner's rationale only works where the properties of the prior art are not known or anticipated. That is not the case here. Given the expectation in the art (including the cited art) that this hypothetical chimeric antibody molecule would retain effector functions, then a direct comparison would only be expected to confirm that the fusion protein recited in the claims possesses unexpected properties. The Examiner has provided no evidence or even speculation otherwise. In essence, to prove that the properties of the combination are ***unexpected***, the Examiner is erroneously requiring Applicants to show that this hypothetical embodiment would have its ***expected*** properties.

Finally, Applicants are ***not required*** to provide any direct comparative evidence to any particular embodiment. It is well settled that indirect evidence is permitted and *must* be considered in making a determination of obviousness or nonobviousness. MPEP §716.02(b)(III). As the predecessor to the Court of Appeals for the Federal Circuit stated, "practical considerations favor allowing the applicant to choose [the embodiment to test]. Prior art devices are sometimes unavailable for testing. They may be disclosed in "paper patents" on inventions which have never been reduced to practice." *Application of Holladay*, 584 F.2d 384 (C.C.P.A. 1978).

For example, in *Application of Fouche*, 439 F.2d 1237 (C.C.P.A. 1971), the applicants relied on an affidavit comparing the claimed compound to a compound that was not the closest prior art, reasoning that his evidence showed that the claimed compound was expected to be superior to the closest prior art compound. The appellate court characterized the applicants' argument as "a kind of indirect showing of unexpected superiority." *Id.* at 1241. In *Fouche*, the examiner and Board maintained the obviousness rejection despite this indirect evidence. The appellate court reversed, concluding that the evidence was sufficient to establish nonobviousness of the claimed compound. Later cases from the Court of Appeals for the Federal Circuit have also explicitly approved of the use of indirect comparative evidence. *See, e.g., In re Grasselli*,713 F.2d 731, 743 (Fed. Cir. 1983) ("'indirect showing of unexpected superiority' sanctioned by precedent") (citing *In re Fenn,* 208 USPQ 470, 473 (CCPA 1981)).

In the present case, Applicants have provided evidence showing that the class of ligand-binding fusion proteins comprising hinge, CH2 and CH3 domains of an immunoglobulin heavy chain were expected to have effector functions and aggregation ability. A number of prior art references, including the Capon Patent cited by the Examiner, confirm this expectation in the prior art. The TNF-binding hypothetical chimeric antibody molecule of the Smith Patent is among this class, and one of ordinary skill in the art would have expected it to retain effector functions and aggregation ability.

The p75 TNFR fusion proteins recited in the instant claims are also among this class, and, similarly, the ordinary skilled person would have expected these fusion proteins to retain effector functions and aggregation ability. In contrast, Applicants have provided

uncontroverted evidence showing that the p75 TNFR fusion proteins encoded and produced by the claimed constructs ***lack the effector functions and aggregation ability that were predicted and expected by the prior art.*** This evidence is exactly the kind of showing of unexpected superiority that was sanctioned by the Federal Circuit in *Grasselli*, and by its predecessor in *Fouche*.

Thus, all of Applicants' evidence must be considered, whether direct or indirect. When the evidence is properly considered, it is clear that the combination recited in the present claims is "more than the predictable use of prior art elements according to their established functions." MPEP §2141(I), citing *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007). As such, the conclusion of nonobviousness is inescapable.

C. Dembic in view of the Smith Patent and the Capon Patent

This rejection was primarily focused on addressing the recitation of SEQ ID NO: 27 in claim 243 or the sequence of claim 233 from HL-60 cells. Page 11 of Action. Dembic, the inventors' own publication, was cited for its teaching of DNA encoding p75 TNFR derived from HL60 cells, which comprises the various peptide fragments recited in the claims. The Smith Patent was cited for teaching DNA encoding p75 TNFR that has the amino acid sequence of SEQ ID NO: 27. The Smith Patent was also cited, as discussed above, for its teaching of a nucleic acid encoding an IgG1/soluble portion of p75 TNFR at col. 10, last paragraph. See Page 11 of the Office Action. The Capon Patent was cited for teaching that the DNA encoding the immunoglobulin portion of the fusion protein can contain at least the hinge, CH2 and CH3 domains of the constant region of a heavy chain.

The reliance on Dembic for its disclosure of TNFR from HL60 cells, and on the Smith Patent for SEQ ID NO: 27, adds nothing to the obviousness rejection discussed immediately above, as Applicants do not dispute that SEQ ID NO: 27 was known, or that TNFR was known to be present on HL60 cells. The arguments explained above thus apply equally to this rejection.

D. Smith Patent in view of Hohmann and Capon Patent

The Smith Patent was cited for its teaching of DNA encoding p75 TNFR of SEQ ID NO: 27 and for teaching the extracellular portion of the p75 TNFR. The Smith Patent was also cited for its teaching of DNA encoding a chimeric antibody molecule described at col. 10, last paragraph, as discussed above. Hohmann was cited for teaching that HL60 cells express p75 TNFR. Page 13 of Office Action. The reliance on Hohmann, which does not teach the sequence of the p75 TNFR expressed by HL60 cells, adds nothing to the obviousness rejection discussed immediately above. The arguments explained above thus apply equally to this rejection.

When considered and given due weight, Appellants' evidence of unexpected results in a multitude of different categories rebuts any possible case of obviousness and requires reversal of the rejection under 35 U.S.C. §103. The evidence shows that the p75 TNFR-Fc fusions encoded and produced by the claimed constructs exhibit unique binding properties, affinity and potency that would not have been expected, and that the immunoglobulin fragments encoded by the claimed polynucleotides exhibit completely different effector properties than those predicted by the prior art.

Supreme Court case law requires that Applicants' claimed invention be deemed nonobvious where, as here, evidence shows that the asserted combination of prior art elements are not carrying out their established functions. "When considering obviousness of a combination of known elements, the operative question is thus 'whether the improvement is more than the predictable use of prior art elements according to their established functions.'" MPEP §2141(I), citing *KSR Intl' Co. v. Teleflex, Inc.* 550 U.S. 398, 417, 82 U.S.P.Q.2d 1385, 1396 (2007).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe the pending claims are in condition for allowance and early notice of thereof is requested.

Dated: March 15, 2011

Respectfully submitted,

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EVIDENCE LIST

Exhibit	Document	Submitted on	Submitted with
A	1990 European priority application	November 22, 2006	Supplemental ADS
B	Declaration of Stewart Lyman Ph.D. under 37 C.F.R. § 1.132	September 8, 2010	Amendment and Response to Office Action
C	Third Declaration of Werner Lesslauer under 37 C.F.R. § 1.132	August 30, 2007	Amendment and Response to Office Action
D	SEQ ID NO: 10 GenBank Search Results	August 30, 2007	Amendment and Response to Office Action
E	ATCC Brochure	September 8, 2010	Amendment and Response to Office Action
F	Fleck *et al. Clin. Vaccine Immunol. 12: 19-27, 2005*	September 8, 2010	Amendment and Response to Office Action
G	Lesslauer Declaration A	December 9, 2004	Amendment and Response to Incomplete Reply to Restriction Requirement
H	Byrn, *Nature*, 344:667-670, April 1990	August 30, 2007	Amendment and Response to Office Action
I	Mohler *et al. J. Immunol.*, 151:1548-1561, 1993	August 30, 2007	Amendment and Response to Office Action
J	Capon *Nature* 337: 525-531, 1989	August 30, 2007	Amendment and Response to Office Action
K	Traunecker, *Nature*, 339:68-70, 1989	August 30, 2007	Amendment and Response to Office Action
L	Kohno *et al.* Presentation 1495, poster 271 presented at American College of Rheumatology Annual Meeting, November 13-17, 2005, San Diego, CA	August 30, 2007	Amendment and Response to Office Action
M	Khare *et al.*, Poster 715 presented at the Annual Meeting of the Society for Investigative Dermatology (SID), May 3 -5, 2006, Philadelphia, PA	August 30, 2007	Amendment and Response to Office Action
N	Barone *et al.*, *Arthritis Rheum.*, v42(9) supplement, September 1999 (S90)	August 30, 2007	Amendment and Response to Office Action
O	Hu et al. Overview of Cell Culture Technology	September 8, 2010	Amendment and Response to Office Action
P	Natsume *et al.* Drug Design Dev. Ther. 3: 7-9, 2009	September 8, 2010	Amendment and Response to Office Action
Q	Enbrel US Product Inert	September 8, 2010	Amendment and Response to Office Action

Exhibit	Document	Submitted on	Submitted with
R	Larsson *et al., FEBS Lett.* 98:333-338, 1979	August 30, 2007	Amendment and Response to Office Action
S	*Fundamental Immunology*, 2nd ed., Paul, ed., Raven Press, New York, 1989, at pages 679-701	August 30, 2007	Amendment and Response to Office Action
T	*Immunology*, 1st ed., Klein ed., Blackwell Scientific Publications, Boston, 1990, pp. 446-447	August 30, 2007	Amendment and Response to Office Action
U	Remicade Product Insert	September 8, 2010	Amendment and Response to Office Action
1	United States Adopted Names (USAN) Council report, *Clin. Pharm. & Ther.*, vol. 66, no. 2, August 1999, at page 209	Concurrently	Supplemental IDS (document D42)
2	Declaration of Taruna Arora under 37 C.F.R. § 1.132	Concurrently	Supplemental IDS (document D15)
3	Winzor *et al.*, *Arch. Biochem. Biophys.*, 268(1): 221-226, 1989	Concurrently	Supplemental IDS (document D40)
4	Wallis *et al. Clin. Inf. Dis.* 38: 1261-1265, 2004	Concurrently	Supplemental IDS (document D38)
5	Wallis *et al. Clin. Inf. Dis.* 41(Suppl 2): S1-S5	Concurrently	Supplemental IDS (document D37)
6	Arora *et al., Cytokine* 45: 124-131, 2009	Concurrently	Supplemental IDS (document D26)
7	Furst *et al. Semin. Arthritis Rheu*m. 36: 159-167, 2006	Concurrently	Supplemental IDS (document D41)
8	Stangfeld *et al., JAMA* 301(7): 737-744, 2009	Concurrently	Supplemental IDS (document D36)